Remarks

Applicant has timely submitted a Request for Continued Examination and this response to the Examiner's Office Action of September 25, 2003. Applicant also submits herewith an Interview Request Form. Applicant respectfully requests the courtesy of a personal interview with the Examiner prior to the next action on the case. Although Applicant has requested an interview in April, with a specific date to be arranged at a later date, Applicant is amenable to any mutually acceptable date.

The Final Office Action dated September 25, 2003 has been carefully reviewed and the foregoing remarks are made in response thereto. In view of the following remarks, Applicant respectfully requests reconsideration and reexamination of this application and the timely allowance of the pending claims.

I. Summary of the Office Action

1. Claims 1-19 and 21-23 are currently pending. Subject to an Examiner's Restriction Requirement, claims 9 and 13-16 have been withdrawn from consideration.

2. Claims 2-4 were rejected under 35 U.S.C. § 112, first paragraph, for purportedly not enabling the claimed invention.

3. Claims 17-19 and 21-23 were rejected under 35 U.S.C. § 112, first paragraph, for purportedly not providing an adequate written description of the claimed invention.

4. Claims 17-19 and 21-23 have been denied benefit of priority to U.S. Provisional Application Serial No. 60/097,846 because claims 17-19 and 21-23 purportedly do not teach a method for treating neurogenic inflammation.

5. Claims 1, 5, 6, and 17-23 were rejected under 35 U.S.C. § 102(e) as purportedly anticipated by U.S. Patent No. 6,063,768 ("First").

6. Claims 1, 5-8, 10-12 and 17-23 were rejected under 35 U.S.C. § 103(a) as purportedly obvious over U.S. Patent No. 6,063,768 ("First") in view of the Merck Manual.

7. Applicants will submit a new Oath or Declaration once allowable claims have been indicated.

8. No claims were allowed.

II. Response to the Office Action

1. Rejection of the claims under 35 U.S.C. § 112, first paragraph, as purportedly not enabled.

Claims 2-4 were rejected under 35 U.S.C. § 112, first paragraph, for purportedly not enabling the claimed invention.

The Examiner has rejected claims 2-4 as purportedly lacking enablement for claims drawn to: 1) methods of reducing inflammation without causing muscle weakness and 2) methods of reducing inflammation comprising an effective dose of botulinum toxin less than 2.5 botulinum units. The Examiner further asserts that the specification purportedly only enables claims drawn to methods of reducing allergy-induced conjunctivitis in a mouse comprising administering botulinum toxin. Applicant respectfully traverse this rejection.

The instant specification discloses methods of treatment that use a chemodenervating agent in a doses that reduce inflammation without causing muscle weakness. (*See, inter allia*, page 4, paragraph 2; "minimum effective doses range from 0.5-5 units as opposed to 20-600 units for treatment of movement disorders. This is because the low dosages regionally block rapid tissue responses characteristic of inflammation..."; *see also,* page 19, paragraph 1; "Minimum doses range between 0.6 units to 15 units and are far lower than that required to produce regional weakness.") Specifically, the specification discloses methods of treatment using doses below 2.5 botulinum toxin units. (*See,* original claim 4)[1]. Consequently, the instant disclosure expressly enables a skilled artisan to treat inflammation, using a chemodenervating agent using a dose that is far lower than that required to produce muscle weakness, and, specifically, at doses below 2.5 botulinum toxin units.

[1] Claims filed in the original specification are part of the disclosure. *In re Benno,* 768 F.2d 1340 (Fed. Cir. 1985).

The Examiner must accept a specification that teaches a skilled artisan how to use the claimed invention as being in compliance with the enablement requirement of § 112, unless there are reasons to doubt the objective truth of the statements relied upon to establish enablement. MPEP § 2164.04. The Examiner has neither questioned nor established any doubt regarding the objective truth of the disclosure.[2] Consequently, the Examiner has not established any reason why the express disclosure of the instant specification should not be accepted as fully satisfying the enablement requirement of § 112.

Although the Examiner has not established reasons to dismiss the express teachings of the instant specification, the Examiner attempts to support his rejection of claims 2-4 by imposing a requirement that the specification actually reduce the claimed invention to practice. (Final Office Action of September 25, 2003; page 5). Specifically, the Examiner dismisses Applicant's arguments and the express disclosure that inflammation can be treated "with a chemodenervative pharmaceutical, such as botulinum toxin, without causing muscle weakness", because "the specification simply does not disclose that said parameter (muscle weakness) was measured." (*Id.*). Also, in the Office Action of July 5, 2001, the Examiner bases the rejection of claims 2-4 under 35 U.S.C. § 112, first paragraph, on a finding that the specification only discloses one example of the claimed methods. Specifically, the Examiner asserts that the specification "discloses only one rat example (CONJUNCTIVITIS) in which the toxin is used at such a low dosage." (Office Action of July 5, 2001 at page 4). Neither of these arguments are legally sufficient to support the Examiner's rejection of the instant claims.

Compliance with the enablement requirement of 35 U.S.C. § 112, first paragraph, however, does not require disclosure of an example. MPEP § 2164.02. In fact, the claimed invention need not be reduced to practice prior to filing. *Gould v. Quigg,* 822 F.2d 1074, 1078 (Fed. Cir. 1987). Examples may be either working or prophetic. MPEP § 2164.02. Consequently, the Examiner cannot properly support a rejection of claims 2-4

[2] "[It is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement." *In re Marzocchi,* 439 F.2d 220, 224 (CCPA 1971).

under § 112, first paragraph, on grounds that muscle weakness, a recited claim element (recited in the current and original claim 2) was not actually measured. Similarly, disclosure of "only one rat example (CONJUNCTIVITIS)"(emphasis added), even if this were factually correct, would also be insufficient grounds to establish *prima facie* nonenablement. Finally, the Examiner appears to object to examples depicted in Figures 8A and 8B, because of "the use of the somewhat vague phrase 'has been demonstrated'" suggests—to the Examiner—that there is no evidence that "said demonstration is actually in the form of an experiment performed as a working example." (Final Office Action of September 25, 2003, page 6). The Examiner speculates that "the employed wording could simply mean that the results of the figures might represent what would be expected to happen if the method of the claims was performed", which, according to the Examiner, means that "this 'example' cannot support the limitations of the claims." (*Id.*). Both this reasoning and conclusion are contrary to well established law and cannot support *prima facie* nonenablement.

The Examiner's reliance on the factually incorrect finding that the instant specification discloses "only one rat example (CONJUNCTIVITIS)" raises three possible grounds for the Examiner's enablement rejection of claims 2-4. Each is legally and factually insufficient to support the instant rejection. First, as discussed above, neither the presence, absence nor number of examples is sufficient to dismiss the express disclosures of a specification. Second, the Examiner appears to derive significance from the alleged fact that the disclosed methods, using low-dose chemodenervating agents were exemplified in "rat" whereas human examples allegedly used doses of 2.5 botulinum units. The specification, however, expressly discloses methods of using chemodenervating agents at doses below 2.5 botulinum units that do not cause muscle weakness. (*See,* above.). The specification also teaches doses above 2.5 botulinum units that are many fold lower than the dose required to treat movement disorders. (*See,* above; especially page 4, paragraph 2 and page 19, paragraph 1). Beyond the Examiner's unsupported conjecture, however, there are no objective reasons provided which support a discounting or dismissal of the express teachings of the instant specification that chemodenervating agents, at doses below 2.5 botulinum units, reduce inflammation

without producing muscle weakness. There is no disclosure that doses of chemodenervating agents below 2.5 botulinum units are limited to rat and the Examiner provides no evidence that supports this speculation.

Finally, the Examiner alleges that the specification enables only the treatment of conjunctivitis in rat, because "only one rat example (CONJUNCTIVITIS)" was disclosed. The Examiner has failed to consider the specification as a whole and instead focuses on a single example to define the enablement of the disclosure. The specification provides 14 pages of examples (pages 10-23). On the final page (page 23), under the heading "New Bioeffect", the Applicant summarizes the observations obtained from the various examples and tests—examples and tests that are not limited to the treatment of conjunctivitis, but instead include treatment of numerous inflammatory conditions, including rheumatoid arthritis (page 19); spasmodic torticollis (page 17); internal inflammatory diseases (page 16); blepharospasm (page 15); allergic blepharoconjunctivitis (page 15); conjunctivitis (pages 13-15); and uticaria (pages 10-13). In summary, the Applicant states:

> The subject invention has been found to rest on a new bioeffect on release of mediators within the denervation field created by a point injection of botulinum toxin which have onset of effect much shorter than the neuromuscular weakening effect. The above offers an explanation as to why beneficial effects are out of proportion to weaknesses created, and explains the different dose response relationships among the various immunotypes of botulinum toxin. (Specification, page 23).

Consequently, the instant specification specifically and expressly teaches that the "new bioeffect" of a chemodenervating agent (reduced inflammation without producing muscle weakness) is not limited to the treatment of conjunctivitis. The Examiner has provided no legal or factual support for this limitation.

In view of the foregoing, Applicant respectfully request that the Examiner withdraw finality and this rejection of claims 2-4.

2. Rejection of the claims under 35 U.S.C. § 112, first paragraph, as purportedly lacking written description.

Claims 17-19 and 21-23 were rejected under 35 U.S.C. § 112, first paragraph, for purportedly not providing an adequate written description of the claimed invention. The Examiner concludes "that the specification cannot support claims amended to recite a method for treating neurogenic inflammation." (Final Office Action of September 25, 2003, page 5). Applicant respectfully traverse this rejection.

The specification does not recite the term "neurogenic inflammation", *per se.* This fact alone, however, does not lead to a conclusion that the specification does not provide adequate written support for the claimed invention. The Examiner has the initial burden of presenting evidence or reasoning that supports a conclusion that a person of ordinary skill in the relevant art would not recognize that the written description provides support for the claims. (MPEP § 2161 (II. A.). The Examiner has failed to meet his burden. The Examiner has failed to provide the necessary evidence or reasoning sufficient to support the rejection of claims 17-19 and 21-23.

Throughout the prosecution of this application, the Examiner has repeatedly dismissed the express teachings of the specification that directly identify nerve cells as a source of inflammation that is treatable by the claimed methods. In each instance, the Examiner has dismissed these disclosures—presented in responsive remarks, argument and in the Declaration of Dr. Martin Aquadro—without basis. The following statements exemplify the Examiner's treatment of portions of the instant specification identified by Applicant and Dr. Aquadro that describe neurogenic inflammation:

- "...the Declarant has quoted every disclosure of the terms 'nerve', 'neural', and 'neurogenically mediated' disclosed in the specification. Said disclosures remain an insufficient written description of the invention as now claimed." (Final Office Action of September 25, 2003, page 3).

- "Regarding the disclosure of 'nerve cell release of histamine'..."[t]he single use of the term 'nerve cell' is insufficient written description for the invention as now claimed." (Final Office Action of September 25, 2003, page 4).

- "Regarding 'neural reflex mechanisms', the above mentioned cite is the only use of the term and this vague disclosure cannot support the invention as now claimed." (Final Office Action of September 25, 2003, page 4).

The unsupported dismissal of the specific and express evidence of written description for the claimed methods in both the specification and the Declaration of Dr. Martin Aquadro suggests that the Examiner is applying a standard that is focused on *ipsis verbis* support for the term "neurogenic inflammation" and not the true legal standard: whether a skilled artisan would recognize that the specification provides written description support for the claimed methods.

In another instance, the Examiner alleges that the specification fails to support the term "neurogenic inflammation, because the specification "discloses that the inflammation of torticollis '*may*' be 'neurogenically mediated'." (Final Office Action of September 25, 2003, page 4). Based on the presence of the word "may", the Examiner again speculates that "Applicant chose not to make a definitive statement regarding the nature of inflammation in even this single embodiment (torticollis). (*Id.*) Based on this speculation, the Examiner concludes that "it cannot now be credibly argued that this minimal disclosure[3] supports claims drawn to a method of treating all forms and embodiments of neurogenic inflammation." (*Id.*) Contrary to this reasoning, the Tenth Edition of Merriam Webster's Collegiate Dictionary, defines "may", *inter allia*, as "having the ability to" and "have power, am able". Consequently the Examiner's interpretation of "may" is speculation, contrary to dictionary meanings of the word and fails to provide a reasoned explanation or evidence why the term "neurogenically mediated", in context, should serve as written description support for "neurogenic inflammation".

The Fifth Unabridged Lawyer's Edition of Stedman's Medical Dictionary defines "neurogenic" as "1. Neurogenous; originating in, starting from, or caused by, the

[3] The Examiner has not defined the quantum of disclosure sufficient to support the term "neurogenic inflammation". Indeed any disclosure, no matter how minimal, is sufficient if a skilled artisan would recognize that the specification provides written description support for the claimed methods. The Examiner has not established any reason why that is not the case here.

nervous system or nerve impulses...". Consequently, the proper inquiry, when determining whether the instant specification provides written description support for the claimed methods of treating "neurogenic inflammation", is not whether the specification provides *ipsis verbis* support, but instead whether it conveys to the skilled artisan that inflammation treatable by administration of a chemodenervating agent includes that inflammation that originates in, starts from or is caused by the central nervous system or nerve cells (nerve impulses). The express disclosures and evidence presented in the specification and the Declaration of Dr. Martin Aquadro—disclosures and evidence that was summarily dismissed by the Examiner—convey exactly that. (*See, for example,* page 5: "The subject anti-inflammatory agent's unique property relates to suppression of the component for the inflammatory response which occurs rapidly, and which is mediated by neural reflex mechanisms"; page 7: "Thus, the subject denervating agent, e.g. botulinum toxin, is demonstrated to achieve a reduction in rapid phase inflammatory responses. The responses are under neural regulation..."). Any rephrasing of this written description support, into the term "neurogenic inflammation", for example, that retains the meaning of the initial disclosure, does not constitute new matter. (MPEP § 2163.07 and *In re Anderson,* 471 F.2d 1237 (CCPA 1973)).Specifically, the mere inclusion of a dictionary or art recognized definition known at the time of filing an application is not considered new matter. (*Id.*).

In view of the foregoing, Applicant respectfully request that the Examiner withdraw finality and this rejection of claims 17-19 and 21-23.

3. **Denial of benefit of priority to U.S. Provisional Application Serial No. 60/097,846**

Claims 17-19 and 21-23 have been denied benefit of priority to U.S. Provisional Application Serial No. 60/097,846 because claims 17-19 and 21-23 purportedly do not teach a method for treating neurogenic inflammation.

Since the Applicant respectfully believe that the instant specification provides an adequate written description for claims 17-19 and 21-23, as discussed in detail above, Applicant respectfully traverse this denial of priority.

4. Rejection of the claims under 35 U.S.C. § 102(e) as purportedly anticipated by First.

Claims 1, 5, 6, and 17-23 were rejected under 35 U.S.C. § 102(e) as purportedly anticipated by U.S. Patent No. 6,063,768 ("First").

Applicant notes that a Request to Declare an Interference with the First patent was submitted on May 14, 2001. Once these claims are determined to be otherwise allowable, the Examiner may determine if an interference should be declared.

5. Rejection of the claims under 35 U.S.C. § 102(e) as purportedly obvious over First in view of the Merck Manual.

Claims 1, 5-8, 10-12 and 17-23 were rejected under 35 U.S.C. § 103(a) as purportedly obvious over U.S. Patent No. 6,063,768 ("First") in view of the Merck Manual.

Applicant notes that a Request to Declare an Interference with the First patent was submitted on May 14, 2001. Once these claims are determined to be otherwise allowable, the Examiner may determine if an interference should be declared.

III. Conclusion.

Applicant believes that the above-reference application is in condition for allowance. Reconsideration and withdrawal of the outstanding rejections and early notice of allowance to that effect is respectfully requested.

EXCEPT for issue fees payable under 37 C.F.R. § 1.18, the Director is hereby authorized by this paper to charge any additional fees during the entire pendency of this application, including fees due under 37 C.F.R. §§ 1.16 and 1.17 which may be required, including any required extension of time fees, or credit any overpayment to Deposit Account No. 13-3250, reference No. 33677.00600. This paragraph is intended to be a **CONSTRUCTIVE PETITION FOR EXTENSION OF TIME** in accordance with 37 C.F. R. § 1.136(a)(3).

If the Examiner finds that a telephone conference would further prosecution of this application, the Examiner is invited to contact the undersigned at 202-835-7553.

Respectfully submitted,

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